



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|----------------------------|-------------|----------------------|---------------------|------------------|
| 10/588,574 | 05/31/2007 | Stig Bengmark | 05822.0340USWO | 8316 |
| 23552 | 7590 | 01/23/2009 | EXAMINER | |
| MERCHANT & GOULD PC | | | ARIANI, KADE | |
| P.O. BOX 2903 | | | ART UNIT | PAPER NUMBER |
| MINNEAPOLIS, MN 55402-0903 | | | 1651 | |
| | | | MAIL DATE | DELIVERY MODE |
| | | | 01/23/2009 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Applicant's reply has overcome the rejection of Claims 12-23 under 35 U.S.C. 112, first paragraph.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, Monte teaches a method for treating a mammal comprising applying a formulation to the mammal comprising probiotics and prebiotics, probiotics comprising *Pediococcus pentosaceus*, *Lactobacillus paracasei*, and *Lactobacillus plantarum*, and 10⁶ or greater probiotic bacteria are introduced, beta-glucan, inulin, pectins, resistant starch, vitamins, amino acids, the formulation in form of tablet or drink (solid or liquid), and 90-90% of prebiotics. Monte teaches probiotics are bacteria that benefit human health, particularly gastrointestinal health (Abstract, page 3 0025, 0028, 0030-0033, page 4 0039, 2nd column 0046, and page 5 0050). Monte further teaches administration of antibiotics, exposure to gamma radiation and X-rays, disease, stress and other disturbances can result in an overgrowth of potentially pathogenic bacteria and/or a decrease in beneficial bacteria (p.2 0013). Monte further teaches certain strains of Lactobacilli have immune-modulating activity (p.2 0015 2nd column).

Monte does not teach *Pediococcus pentosaceus* 16:1(LMG P-20608), *Leuconostoc mesenteriodes* 23-77:1 (LMG P-20607), *Lactobacillus paracasei* subsp *paracasei* F-19 (LMG P-17086), and *Lactobacillus plantarum* 2362 (LMG P-20606), and

Art Unit: 1651

a stress-induced inflammatory disorder. However, Kruszewskya et al. teach *Pediococcus pentosaceus* 16:1, *Leuconostoc mesenteriodes* 77:1, *Lactobacillus paracasei* subsp *paracasei* F-19, and *Lactobacillus plantarum* 2592 (Abstract, page 41 Table 2.). Kruszewskya et al. further teach exposure of *Lactobacillus* strains to pH 5 for 1 hour induced *de novo* production of several proteins, five of which cross-reacted with stress proteins and may protect other surface proteins and adhesions during transport (Abstract). Kruszewskya et al. teach production of antimicrobial substances with activity against other bacteria, induced induction of anti-inflammatory cytokines (IL-10) by *L. paracasei* subsp *paracasei* F-19, and teach, *Lactobacillus plantarum* 2592, *Pediococcus pentosaceus* 16:1, produced antioxidants which provide beneficial effects in scavenging free radicals (Abstract and p.45 1st and 2nd columns). Kruszewskya et al. teach the strains ferment fibers and exert beneficial effect of the colonic flora and bowel function (p.44 2nd column 2nd paragraph), and produce β -galactosidase to alleviate lactose intolerance, and produce bacteriocins with bactericidal effect against bacterial species like *H. pylori* (p.44 1st column 2nd and 3rd paragraphs). The LAB strains taught by Kruszewskya et al. are the same or in the case of *Lactobacillus plantarum* 2592, an obvious variant of the claimed LAB strains. Thus, Kruszewskya et al. teach and suggest the claimed LAB strains.

Further motivation to use a combination of probiotic strains is in Kaur et al. who teach a preparation comprising multiple strains of probiotics (combination of probiotic strains) for treating ulcerative colitis (stress-induced inflammation) (p.4 Table 1. VSL#3). Kaur et al. further teach synbiotics (a mixture of probiotics and prebiotics) overcome the

Art Unit: 1651

limitations of probiotics and improve the survival and implantation of live microbial dietary supplement (p.7 2nd column 2nd paragraph). Kaur et al. also teach immunomodulation by probiotics (p.5 1st and 2nd columns).

Furthermore, Zhang et al. teach a characteristic feature of inflammation is the peroxidation of lipids and formation of lipid peroxidation products, which has been linked to cellular dysfunction. Zhang et al. teach myeloperoxidase (MPO) major role in formation of bioactive lipid oxidation products and promoting oxidative stress during inflammation (see Abstract and Introduction, p.46121 1st column end paragraph and 2nd column lines 1-4).

Therefore, in view of the above teachings, a person of ordinary skill in the art at the time the invention was made could have been motivated the art to use *Lactobacillus* strains as taught by Kruszewskya et al. in the method of Monte with predictable results of producing anti-inflammatory cytokines, antioxidants, and to ferment fibers and exert beneficial effect of the colonic flora and bowel function, produce β -galactosidase to alleviate lactose intolerance order to provide a method for treating a stress-induced inflammatory disorder comprising applying to the mammal a formulation comprising *Pediococcus pentosaceus* 16:1, *Leuconostoc mesenteriodes* 23-77:1, *lactobacillus paracasei subsp paracasei* F-19, and *Lactobacillus plantarum* 2362, and fibers (prebiotics). The motivation to administer a formulation comprising probiotics and prebiotics for preventing a stress-induced disorder as taught by Kruszewskya et al. and Kaur et al. would be the production of anti-inflammatory cytokines and antioxidants (to

Art Unit: 1651

protect against free radical injury), and beneficial effect on the colonic flora by the probiotic strains.

Applicant argues that while Kruszewskya discloses each of the noted strains, it does not teach or suggest a formulation comprising all four of strains as recited in pending claims.

However, Kruszewskya teach the selected LAB strains have shown to survive and multiply during the acid and bile stress conditions of human stomach and upper intestine and they have a prominent ability to colonise the human large intestine, (p.43 2nd column last paragraph and p.44 1st column 1st paragraph). Kruszewskya teach LAB have a GRAS (generally regarded as safe) status, and have been widely used in food industry and there is an increasing interest to add selected strains to food items to treat various diseases, such as infections, allergy, inflammatory bowel disease, and cancer (p.43 1st column 1st paragraph).

Moreover, as mentioned immediately above, Kaur et al. teach a probiotic preparation comprising multiple strains of probiotic strains for treating ulcerative colitis (an stress-induced inflammation) (p.4 Table 1., VSL#3). Kaur et al. further teach synbiotics (a mixture of probiotics and prebiotics) overcome the limitations of probiotics and improve the survival and implantation of live microbial dietary supplement (p.7 2nd column 2nd paragraph).

Therefore, a person of ordinary skill in the art at the time the invention was made could have been motivated to administer a combination of the four strains as taught by Kruszewskya and the results would have been predictable. As indicated in MPEP "It is

Art Unit: 1651

prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted).

Applicant argues that a person of ordinary skill in the art would have not been motivated to include *Leuconostoc mesenteroides* 23-77:1, because there is no data in Kruszewskya supporting the production of anti-inflammatory cytokines.

However, as mentioned immediately above, Kruszewskya teaches the tetsted strains ferment fibers and they should exert a benebeficial effect on the colonic flora and possibly act as a prebiotic since they fermnet inulin,a nondigestible fructan, which has been shown to stimulate the growth of Bifidobacteria (p.44 2nd column 2nd paragraph). Thus, a perosn of ordinary skill in the art at the time the invention was made could have been motivated to use the strains for their ability to ferment fibers and as a prebiotc.

Applicant argues that the production of pro-inflammtory cytokine IL-8 by *lactobacillus paracasei subsp paracasei F-19* as taught by Kruszewskya, would discouraged a person of ordinary skill in the art to even consider including *lactobacillus paracasei subsp paracasei F-19* in a formulation to be used to treat stress-induced inflammatory disorder.

However, Kruszewskya teaches a mild immunostimulatory effect was exerted by *lactobacillus paracasei subsp paracasei F-19* (p.45 1st column 2nd paragraph lines 1-4), it must also be noted that IL-8 is a mediator of the immune reaction in the innate

Art Unit: 1651

immune system response which provide immediate defense against infection and is not long lasting. Moreover, Kaur et al. teach it is a well-established fact that by probiotic therapy resistant to pathogen and immune stimulation (non-specific immune response) can be achieved (p.7 1st column last paragraph, and p.5 2nd column 2nd paragraph).

Thus, a person of ordinary skill in the art at the time the invention was made could have motivated to use the immune stimulation exerted by *lactobacillus paracasei subsp paracasei F-19* in order to provide resistant to pathogens.